Natural history and outcomes in drug induced autoimmune hepatitis

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Natural History And Outcomes In Drug Induced Autoimmune Hepatitis

Short title Drug induced autoimmune hepatitis

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Abbreviations

AIH autoimmune hepatitis, DIAIH drug induced autoimmune hepatitis, RUCAM Roussel Uclaf Causality Assessment Method, LT liver transplant, LRM liver related mortality, DILIN Drug Induced Liver Injury Network,

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Author contribution

TY data collection and writing first draft, KHJL data analysis and writing first draft, SG statistical support, NP intellectual content and critical revisions, SV data collection, study concept and design, intellectual content and critical revisions. All co-authors contributed to and reviewed the final draft of the manuscript. SV is the guarantor of the manuscript

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Abstract

Background and aims: Drug induced autoimmune hepatitis (DIAIH) remains poorly characterised**.** Our aim was to assess natural history and outcomes in DIAIH.

Methods: Retrospective cohort study.

Results: Eighty-two patients with AIH identified, 11 (13.4 %) having DIAIH, implicated drugs being nitrofurantoin (n=4), statins (n=4), herbal remedies (n=2), and diclofenac (n=1). Female gender (81.8% vs. 80.3%), acute onset (54.5% vs. 46.5%), elevated serum globulins/IgG (72.7% vs. 75.4%), fibrosis stage (Ishak) (2.8 $\pm$1.8 vs. 3.6 $\pm$2.0), cirrhosis at onset (27.2% vs. 35.2%), moderate-severe portal inflammation (81.8% vs. 82.2%), interface (54.5% vs. 63.9%) and lobular hepatitis (63.6% vs. 59%), remission (100% vs. 92.4%), relapse (60% vs. 83.3%) and poor outcome (18.2% vs. 36.6%) were similar in those with DIAIH and AIH ($p>0.05$). The former were however more likely to be aged $\geq$ 60 yrs (72.7% vs. 40.8%), and take longer to relapse on immunosuppression discontinuation [131(37-216) vs. 14 (1-155) wks] ($p=/<0.05$). On KM analysis probability of poor outcome was similar in those with DIAIH and AIH (log rank test 0.339). On comparing those with (n=4) and without nitrofurantoin (n=7) DIAIH, the former were older (76.7$\pm$ 3.9 vs. 53.6 $\pm$ 25.3 yrs), have longer duration of drug use prior to DIAIH diagnosis (36.0 $\pm$9.4 vs. 14.5 $\pm$12.7 mths), higher fibrosis stage (3.75 $\pm$2.1 vs. 2.3 $\pm$1.6) and less likely to relapse (0% vs. 100%) upon immunosuppression discontinuation.

Conclusions: About 15% of patients with AIH have DIAIH with similar outcomes though the latter are older with a propensity for late relapse, mandating long-term follow up.

Key words: drug induced liver injury, nitrofurantoin, statins, herbal remedies

Introduction

Autoimmune hepatitis (AIH) is a chronic disorder of unknown aetiology characterised by presence of autoantibodies, hypergammaglobulinaemia, and interface hepatitis with about 85% showing an excellent response to immunosuppression (1,2).

A number of factors predict outcome in AIH including presence of cirrhosis, normal transaminases during follow up and ethnicity (3-6). Despite increasing interest in drug induced AIH (DIAIH), this remains an uncharacterised cohort with lack of consensus regarding diagnostic criteria, need for long-term immunosuppression and outcomes (7-11). This is mainly due to difficulty in differentiating between drug induced liver injury (DILI), immune DILI, DIAIH and coincidental drug use. Another contributing factor is that patients presenting with DILI can eventually develop AIH after varying periods of latency (11-13). The natural history of DIAIH is therefore controversial with some suggesting a benign course (absence of hepatic fibrosis and no relapse after immunosuppression discontinuation) (8), with others reporting advanced hepatic fibrosis and failure to maintain remission after discontinuation of prednisolone/azathioprine (7).

The aim of this study therefore was to assess natural history and outcomes in patients with DIAIH and to further stratify natural history of DIAIH depending on the nature of the culprit drug.

Patients and methods

This retrospective cohort study included all patients with AIH being followed up between Jan 2005 and Oct 2013 at a teaching hospital in southeast England, with last follow up recorded as of June 2014. Patients were identified via the electronic histopathology and clinic letters databases.

Autoimmune hepatitis was defined by criteria established by the International Autoimmune Hepatitis Group (14).

Study definitions

• DIAIH:

- Normal liver tests (if available) prior to drug initiation
- No pre existing liver disease
- Definite temporal association between drug initiation and subsequent diagnosis of AIH
- Other causes for liver disease diligently excluded
- Probable or definite by revised AIH criteria (14)
- Roussel Uclaf Causality Assessment Method (RUCAM) score of highly probable (>8) or probable (6-8)(15)

• Acute presentation: Bilirubin ≥ 5xULN and or ALT > 1000 IU/L.

• Liver failure: Presence of any degree of hepatic encephalopathy and or international normalised ration (INR) ≥ 2

• Remission: Normal ALT/resolution of symptoms, and if available normal IgG and histology

• Relapse: ALT ≥ 2ULN with/without symptoms on treatment discontinuation

• Poor outcome: Failure to achieve remission, liver failure (either at initial presentation or follow up), development of cirrhosis during follow up, development of cirrhosis complications, need for liver transplantation (LT) and/or liver related mortality (LRM).

Cirrhosis related complications were defined as any one or more of the following: ascites/spontaneous bacterial peritonitis, high risk varices/variceal bleed, hepatocellular cancer and hepatic encephalopathy

The exclusion criteria were

• Overlap syndrome including biliary pathology such as primary biliary cirrhosis,

primary sclerosing cholangitis and autoimmune cholangitis.

• Co existing liver disease due to alcohol, viral hepatitis, non-alcoholic fatty liver disease

• Incomplete medical records

A detailed review of the medical records (medical notes and electronic pathology and radiology database) was performed for those considered to have AIH and for each patient the following data was collected anonymously: demographics, autoantibodies (ANA, SMA, AMA, LKM), hepatitis serology, alcohol history, autoimmune hepatitis score [assessed by revised International Autoimmune Hepatitis Club diagnostic criteria (14), dose and duration of culprit drug (in cases of DIAIH), liver tests at onset, during remission and at last follow up and presence of additional autoimmune conditions.

The liver biopsy report for each individual was reviewed and the following data collected: fibrosis stage (Ishak), presence of portal and lobular inflammation, and interface hepatitis, (all classified semi quantitatively as mild, moderate or severe), portal and lobular plasma cells, lymphocytes, neutrophils and eosinophils, collapse, necrosis, cholestasis and rosettes (all as yes/no).

In those individuals where the initial liver biopsy report was incomplete or unavailable, the biopsies were re reviewed by a dedicated local pathologist (MH) (see acknowledgement)

Statistical analysis

Data are presented as mean ±standard deviation, median (interquartile range) or number (%) and all reported p values are two-tailed. The Mann-Whitney U and Student's t tests were used to compare non-parametric and parametric continuous variables respectively and categorical data were compared using the χ^2 test/Fisher exact test. Kaplan-Meier (KM) curves were generated to assess probability of poor outcome in those with DIAIH and AIH. Statistical analyses were undertaken using SPSS Version 22 (Armonk, NY, IBM Corp).

This study was classified as service evaluation by our Internal Institutional Ethical

Sponsorship Group and hence they determined that individual patient consent and formal National Research Ethics Approval were unnecessary.

Results

During the study period 109 potential patients were identified. Of these 27 were excluded as: presence of overlap syndrome/biliary (n=17), coexisting liver disease (n=3)(non-alcoholic fatty liver disease n=2, chronic hepatitis C, n=1), drug induced liver injury (n=2), positive hepatitis E serology (n=1), and medical records not available (n=4). Eighty-two were therefore found suitable for the study. In 33(40.2%) the initial diagnosis of AIH had been made prior to 2005.

Table 1 shows the demographic data at entry in the whole cohort. Those with a positive autoantibody included 57 with positive ANA/SMA (one also LKM positive) and one with isolated positive LKM and one with liver cytosol antibody. In 80 patients data was available to calculate pre treatment AIH scores: 35 (43.7%) were definite and 37 (46.2%) probable AIH. Seventy-six (92.7%) patients were treated of whom 71 (93.4%) achieved remission. Of the six not treated (table 1) three had mild disease (included one with DIAIH who achieved spontaneous remission), three had likely "burnt out AIH" of whom one presented with variceal bleeding necessitating a portocaval shunt, one underwent a LT, and one was listed for LT then delisted as stabilised (but eventually died). The median follow up for the whole cohort was 86.3 $\pm$61.8 mths with only 12 (14.6%) having < 18 mths follow up.

All but two patients had undergone a liver biopsy at initial presentation. These two included a seventy-nine years old man with a pretreatment AIH score of 12 (biopsy attempted but unsuccessful) and a 13 year old with pretreatment AIH score of 17 (coagulopathy precluded biopsy). The original biopsy reports and liver biopsy samples were available in 72/80 (90 %) and 70/80 (78.7%) patients respectively. In the eight with no liver biopsy report available, the initial diagnosis had been made at an outside hospital of whom in four (50%) this was at a

regional transplant centre. Sixty of the 72 biopsies (83.3%) biopsies had either been reviewed by a dedicated local hisopathologist (MH) and or by two dedicated hisptopathologists (BP and AK) at the regional transplant centre (see acknowledgement). This included ten biopsies that were re reviewed by the local dedicated histopathologist (MH) as the original report was incomplete.

Data in patients with DIAIH and AIH.

Of the 82 patients identified with AIH, 11 (13.4%) were considered to have DIAIH (table 2). RUCAM scores were probable for all 11 cases ranging between 6-8 (table 2). The implicated drugs were nitrofurantoin (n=4), statins (n=4), herbal remedies (n=2), and diclofenac (n=1). The herbal remedies included Echinacea (used for the common cold) and valerian (used for insomnia). All but two (18.1%) patients with DIAIH were female. In eight (72.7%), baseline liver tests were normal prior to initiation of the offending drug, these being unavailable in three patients. Hepatitis E serology was available in six (all negative). Seventy percent with DIAIH had elevated IgG. The mean duration of drug use prior to diagnosis of DIAIH was 23.1 $\pm$15.6 mths. Eosinophilia was not reported in any of the 11 patients though two (patient no 4 and 11) developed a transient rash after use of concomitant drugs (salazopyrin and unknown antibiotic). However both already had symptoms/abnormal liver tests at time of initiation of the concomitant drugs.

Table 3 shows data in those with and DIAIH and AIH. The former were more likely to be $\geq$ 60 years at presentation (p=0.048), score as probable AIH on revised criteria (p=0.012), and take longer time to relapse after discontinuation of immunosuppression (p=0.038). There were no significant differences as regards gender, liver tests at presentation, acute presentation, presence of other autoimmune conditions, symptoms, fibrosis stage and cirrhosis at onset, presence of portal/lobular inflammation, interface hepatitis, plasma cells, lymphocytes, eosinophils, neutrophils, collapse, cholestasis, rosettes and treatment schedules

(p>0.05)(table 3). In 17/76 (22.4%) treated patients (two with DIAIH) additional drugs were used: 6-mercaptopurine (n=11, due to azathioprine intolerance); mycophenolate(n= 5, in two azathioprine intolerance and in three suboptimal response to azathioprine); and cyclosporine (n=1, suboptimal response to azathioprine).

In the AIH and DIAIH groups, median dose of prednisolone at onset was 30mg (5– 60) and 30 mg (10-40), (p=0.133) and 7.00mg (2.50 – 40) and 15.0mg (5 – 40) at last follow-up respectively (p=0.031). Similarly, in the AIH and DIAIH groups, the median dose of azathioprine at onset was 50mg (50 – 150) and 50mg (50 – 100) (p=0.616) and 50mg (50 – 200) and 50mg (50 – 100) at last follow-up respectively (p=0.572).

Forty-two (51.2%) had other extra hepatic autoimmune disorders, though the prevalence was no different in those with DIAIH and AIH (table 3). These included thyroid disease(n=22), rheumatological conditions (n=13), dermatological disorders(n=3), autoimmune haemolytic anaemia n=2, gastrointestinal (ulcerative colitis/celiac disease, n=3), vasculitis (Churg-Strauss/temporal arteritis, n=2) and extrinsic allergic alveolitis n=1. Four (9.52%) had more than one extra hepatic autoimmune condition. Of the five patients with DIAIH and additional autoimmune conditions three had thyroid disease.

Patients with nitrofurantion and non- nitrofurantoin DIAIH

Comparing those with (n=4) and without nitrofurantoin (n=7) DIAIH, the former were older and had lower ALT but higher fibrosis stage at presentation. The duration between drug initiation and detection of abnormal liver tests and duration between detection of abnormal liver tests and specialist review was longer in those with nitrofurantoin DIAIH. In all four cases with nitrofurantoin DIAIH, the drug was only discontinued after specialist review. This was in contrast to the non-nitrofurantoin group where in 74.1% (statins n=4 and diclofenac n=1) the drugs were discontinued by primary care physicians upon receipt of abnormal liver

tests (table 5). Despite shorter duration of immunosuppression prior to discontinuation none of the patients with nitrofurantoin DIAIH relapsed compared to all in the non-nitrofurantoin group (table 5).

Outcomes

Overall 28 (34.1%) patients had a poor outcome (table 3 and 4). This included six (7.3%) with liver failure at onset of whom two also had cirrhosis, six (7.3%) developing cirrhosis during follow up (confirmed histologically in five and radiologically in one), fifteen (18.3%) developing cirrhosis related complications (ascites n=9, hepatic encephalopathy, n= 3, variceal bleeding/high risk varices, n= 6), five (6.5%) failing to achieve remission and two (2.4%) undergoing LT (some had more than one event). Of those with cirrhosis related complications, 12 developed them at presentation and the remaining three during follow up. There were seven deaths (8.5%), one in DIAIH group, (non-LRM) and six in AIH group of which five (83.3%) were liver related.

The two with DIAH and a poor outcome were an 82 year old lady with nitrofurantoin induced AIH (patient no 1) who had cirrhosis and ascites at onset (resolved with immunosuppression) with a non-LRM and a 19 year old with diclofenac induced AIH (patient no 4) who presented with acute liver failure (INR of 2.2), was transferred to the regional transplant centre but responded to medical treatment. Prevalence of poor outcome was lower in those with DIAIH (2/11, 18.2%) vs. those with AIH (26/71, 36.6%) though the differences were not statistically significant. However, none of the patients with DIAIH failed to achieve remission, developed cirrhosis during follow up, needed a LT or had a LRM (table 4). Thirty patients (36.6%), 27 with AIH and three with DIAIH had undergone more than one liver biopsy after a median interval of 30 mths (6-288). Overall 18 (60.0%) had stable fibrosis, five (16.7%) had reduction in fibrosis and seven (23.3%) had fibrosis progression- 0/3 (0%) with DIAIH and 7/26 (26.9%) with AIH (p=0.548). Even if just development of cirrhosis and need for LT

were considered as poor outcome there was still no statistically significant difference between those with DIAIH [0/11 (0%)] and AIH [8/71 (11.27%)] (p=0.241).

KM analysis showed that probability of a poor outcome was no different in those with DIAIH and AIH (log rank test 0.339) (fig 1).

Discussion

In this retrospective cohort study we observed that approximately 15% of patients with AIH had DIAIH, the implicated drugs in three fourths being either nitrofurantoin or statins with herbal medication accounting for ~ 20% of the cases. The diagnosis of DIAIH was robustly made with all patients scoring as probable on the RUCAM scale. The natural history was similar in DIAIH and AIH especially as regards clinical presentation, presence of hepatic fibrosis, prevalence of cirrhosis and poor outcomes, and relapse rates. However, those with DIAIH were older (75% being above the age of 60 yrs), with a propensity for late relapse. This was despite those with DIAIH having a higher dose of prednisolone at last follow up. Finally, compared to the non-nitrofurantoin group, those with nitrofurantoin related DIAIH had more advanced fibrosis at presentation but lower risk of relapse on immunosuppression discontinuation. Increasing age is an established risk factor for DILI as also confirmed by Bjornsson et al's recent population based study, where a two fold increase in crude annual incidence of DILI (19.1- 39.9 /100,000) was observed in those < 25 yrs vs. > 70 yrs (16). Drug dosage also predisposes to DILI and in the aforementioned study, 88% with DILI received daily doses > 50 mgs (16) compared with 75% of our cohort.

Implicated drugs in this study [(nitrofurantoin, statins, diclofenac, and herbal remedies (echinacea, valerian)] have all previously been reported to cause DILI/DIAIH (17-28). Our reported frequency of DIAIH (13.4%) is consistent with earlier studies (9.2-12%) (7,8). However, differentiating DIAIH from DILI or immune DILI can be challenging clinically

and histologically. Suzuki et al reported that interface hepatitis, focal necrosis and portal inflammation, portal and intraacinar plasma cells, rosette formation and emperipolesis favoured AIH with portal neutrophils and intracellular cholestasis favouring DILI (29). However they observed indistinguishable histological features in AIH and DIAIH, which is consistent with our observation. Nonetheless, it must be noted that Suzuki et al observed poor concordance amongst four experienced histopathologists for DIAIH (28.5%) compared to concordance of 46.4% for AIH, 42.1% for DILI (hepatocellular) and 50% for DILI (cholestatic/mixed) (29). Immune DILI and DIAIH are also indistinguishable clinically, though the former may be associated with a rash, eosinophilia, absence of hepatic fibrosis and lack of relapse on immunosuppression discontinuation (10).

Suzuki et al and Bjornsson et al's data (8,29) does however suggest that the main histological feature that might differentiate AIH and DIAIH is lack of advanced fibrosis (>metavir F2) in the latter. However we could not corroborate this as mean fibrosis stage (2.8 ±1.8 vs. 3.6 ±2.0) and cirrhosis at presentation (27.2% vs. 35.2%) were no different in those with DIAIH and AIH. Even taking into account the six AIH patients that developed cirrhosis during follow up, the overall prevalence [3/11 (27.2%) vs. 31/71) (43.6%)] was still not statistically different in those with DIAIH and AIH. A possible explanation for these divergent results maybe that our patients were at least a decade older than Suzuki et and Bjornsson et al's cohort (8,29) and advanced age is a predictor of more advanced hepatic fibrosis. However, Heurgue et al observed similar prevalence (57% vs. 48%) of F3-F4 fibrosis (metavir) in DIAIH and AIH despite a mean age of 47 years (7). Appleyard et al (17) and the Spanish registry of Hepatotoxicity (30) have also reported presence of cirrhosis in DIAIH. Finally, in two recent reviews that included more than 100 cases of nitrofurantoin related DILI cirrhosis was not infrequently observed (18,19). These data suggest that advanced hepatic fibrosis can be observed in DIAIH and should not negate against its diagnosis.

Another factor stated to differentiate DIAIH and AIH is lack of relapse upon discontinuation of immunosuppression in the former (8). Our relapse rates, though lower in DIAIH (60% vs. 83.3%) were not statistically different compared to the AIH group. Heurgue et al also reported a relapse rate of 42.8% in their cohort with DIAIH (7). In contrast, Bjornsson et al reported no relapses in 20 patients with DIAIH (included 11 with nitrofurnatoin and 9 with minocycline) (8), though it is conceivable that at least some had immune DILI where relapses are less likely (8,10). Additionally, the duration of follow up was uncertain in Bjornsson et al's study (8). This maybe of relevance in view of our data showing a tendency for late relapse in DIAIH. Sugimoto et al have also reported seven DILI cases where liver tests did improve spontaneously upon cessation of the offending drug, with a subsequent flare that necessitated steroid treatment (11). Furthermore, Bjornsson et al observed AIH developing in 22% after a mean of 5.8 years post hospitalisation with DILI (12). These data suggest that in patients with DILI/DIAIH, normalisation of liver tests (either spontaneously or after use of immunosuppression) does not guarantee a benign course and highlights the need for prolonged follow up.

Stains and nitrofurantoin can cause both hepatocellular and cholestatic DILI as will as DIAIH (17-22). In a recent publication by the Drug Induced Liver Injury Network (DILIN), of the 22 patients identified with statin induced DILI, 6 (27.2%) were considered to have DIAIH (20). They were older than those with hepatocellular DILI (62 $\pm$10.3) vs. 53 $\pm$9.8) with half requiring immunosuppression and documented relapse in at least one patient. About 50% had been on a statin for longer than 12 months, consistent with our data (duration of statin use 9-36 months). In two reviews on nitrofurantoin DILI (19,20), 50% were above the age of 60 yrs, and 54% had taken the drug for two years or longer with six deaths and one patient undergoing LT. Bjornnson et al's recent study observed DILI in 1:1369 patients using nitoufurantoin, confirming that this drug is a rare yet serious cause of hepatotoxicity (16).

We observed distinct differences between those with nitrofurantoin and non-nitrofurnatoin DIAIH. The former had longer duration of drug use prior to detection of abnormal liver tests and on going drug use despite abnormal liver tests, factors associated with more severe DILI (31). This might be another explanation for the high prevalence of cirrhosis (50%) in this cohort. Interestingly all relapses occurred in the non-nitrofurantoin group though at present we are unable to offer an explanation for this.

Our 20% prevalence of DIAIH due to herbal remedies is consistent with recent DILIN data where herbal and dietary supplements accounted for 15.5% of the DILI cases, the prevalence however significantly increasing from 7% to 20% during the study period (2004-2013) (32). Valerian is a common herbal medication that is used to treat insomnia and a recent US survey showed about 5.6% of adults having used it in the past year (33). In 1989 MacGregor et al first reported valerian associated hepatotoxicity in a case series of 4 patients (of whom one had advanced fibrosis) (25), this being followed by another case report (26). There have been warnings to avoid valerian in individuals with liver disease (34). There are two prior case reports of Echinacea associated hepatotoxicity including one with positive autoantibodies (27, 28). This study additionally highlights lack of awareness amongst healthcare professionals about the hepatotoxic potential of nitrofurantoin and herbal remedies as despite detection of abnormal liver tests both drugs were discontinued only after specialist review.

Though prevalence of poor outcome was lower in those with DIAIH (18.2 vs. 36.6%), this was not statistically different, as was also supported by the KM analysis. However it is noteworthy that none with DIAIH failed to achieve remission, develop fibrosis progression, needed a LT and or had a liver related mortality.

In conclusion the natural history of DIAIH appears to be similar to AIH especially as regards presence of advanced fibrosis at presentation and inability to maintain remission on

immunosuppression withdrawal, especially in the non-nitrofurantoin group. These data suggest that at least some patients with DIAIH mandate long-term follow up. Nonetheless, this needs corroboration by larger prospective studies.

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Fig 1. KM analysis showing probability of poor outcome in those with AIH and DIAIH

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Table 1. Data at entry in the whole cohort (n = 82)

Age (yrs)	**55.40 ±16.54**
>60 years	**37 (45.1%)**
Caucasian	78 (95.1%)
Female	66 (80.5%)
Body mass index (kg/m^2)	26.46 ±5.10
Symptoms	68/79 (86.1%)
Autoantibody positive	59/81 (72.8 %)
ANA/SMA ≥80	50/76 (65.8%)
Bilirubin (mg/dl)	47.00 (5 – 530)
ALT (iu/l)	480.00 (37 – 3480)
Alkaline phosphatase (iu/l)	221.6 ± 114.0
Albumin (g/l)	37.1 ± 7.2
Globulins (g/l)	43.6 ± 12.0
Immunoglobulins	23.8 ± 10.7
Platelet count	227.7 ± 107.1
Acute presentation	35 (42.7%)
Fibrosis stage (index biopsy)	3.47 ±2.01
Cirrhosis at onset	28 (34.1%)
Drug induced autoimmune hepatitis	11 (13.4%)
Treated	76 (92.7%)
Remission	71 (93.4%)
Immmunosuppression discontinued	17 (20.7%)
Treatment duration before discontinuation (mths)	20.1 ±11.2
Relapse	13/17 (76.4%)
Poor outcome	28 (34.1%)
Other autoimmune conditions	42/81 (51.8%)

Table 2: Data in patients with drug induced autoimmune hepatitis

No Age/ Sex	Drug ,dose, duration	ANA/ SMA	AIH Score	Bilirubin mol/l	ALT iu/l	INR	Fibrosis stage (Ishak)	RUCAM score	Treatment	Treatment stopped
1 82F	Nitrofurantoin 50 mg 35 mths	1:640	12	32	115	1.2	6	8	prednisolone and azathioprine	yes after 12 mths, no relapse
2 75F	Nitrofurantoin 50 mgs, 36 mths	1:1280	10	94	587	1.5	5	7	prednisolone then azathioprine	yes after 17 mths, no relapse
3 73M	Nitrofurantoin 100 mg 48 mths	- ve	10	15	178	1.1	2	8	prednisolone then azathioprine/ 6MP	no
4 19F	Diclofenac, 50 mg thrice daily 2 mths	1:320	11	461	3480	2.2	1	8	prednisolone and azathioprine	no
5 63F	Simvastatin* 18 mths	-ve	11	15	1245	1.3	5	8	prednisolone then azathioprine	no
6 73F	Atorvastatin 20 mgs 9 mths	1:640	15	10	721	1	2	8	None, spontaneous remission	
7 56/M	Echinacea dose/ duration unknown	1:640	12	258	1200	1.1	4	6	prednisolone then azathiorpine	yes after 36 mths, relapsed and re treated
8 69F	Simvastatin, dose unknown 36 mths	1:200	16	21	314	1	1	8	Prednisolone only	yes after 16 mths, relapsed and retreated
9 78F	Atorvastatin 20 mg 19 mths	1:640	17	45	640	1.1	2	8	Prednisolone only	yes after 24 mths , relapsed and retreated
10 17F	Valerian, dose unknown 3 months	1:320	12	69	1468	1.1	1	7	prednisolone then azathioprine	no
11 77F	Nitrofurantoin 50-100 mgs 25 mths	- ve	14	116	429	1.1	2	8	prednisolone then azathioprine/ 6MP	no

* In a drug trial so received either 20 mg or 80mg simvastatin

Table 3. Data in patients with drug induced autoimmune hepatitis (DIAIH) and autoimmune hepatitis (AIH)

	DIAIH (n=11)	**AIH (n=71)**	**P value**
Female	9 (81.8%)	57 (80.3%)	0.635
Age	55.04 ±15.2	62.0 ±22.9	0.156
Age ≥ 60 years	8 (72.7%)	29 (40.8%)	0.049
BMI	24.3 + 5.14	26.9 + 6.11	0.200
Other AI conditions	5 (45.4%)	37/70 (52.8%)	0.447
Acute presentation	6 (54.5%)	33 (46.5%)	0.618
Symptoms	11 (100%)	57/68 (83.8%)	0.170
Duration of symptoms (days)	84.0 (3 – 120)	23.0 (1 – 728)	0.185
Duration between abnormal liver tests and specialist review (wks)	8 (0.5-40)	6 (0.14-140)	
Definite AIH pre treatment	2 (18.2%)	33/69 (47.8%)	0.062
Probable AIH pre treatment	9 (81.8%)	28/69 (40.5%)	0.012
Billirubin (µmol/dl)			
at entry	57.0 (15 – 461)	51.0 (5 – 481)	0.874
at remission	12 (9-23)	8(4-38)	0.428
ALT (iu/l)			
at entry	613.0 (115 – 3480)	512.0 (37 – 2990)	0.324
at remission	29.9 ±12.0	27.1 ±11.7	0.635
ALT/AST > 10 ULN	8 (72.7)	35 (49.2%)	0.160
ALP (iu/l)			
at entry	268.2 ±149.1	214.8 ±142.9	0.250
at remission	86.4.0 ± 37.7	88.3 ± 48.2	0.908
Globulin (g/dl)			
at entry	40.4 ±6.5	44.0 ±12.4	0.455
at remission	30.3 ± 4.7	32.8 ± 9.3	0.433
IgG (g/L)			
at entry	21.4 ±7.5	24.3 ±11.2	0.422
at remission	11.1 ±2.2	12.8 ±3.2	0.193
Globulins/IgG elevated at onset	8/11 (72.7%)	52/69 (75.4%)	0.851
Albumin (g/L)			
at entry	36.1 ±5.1	36.7 ±7.1	0.798
at remission	39.4 ±4.0	41.2 ±4.9	0.250
INR			
at entry	1.2 ±0.3	1.3 ±0.3	0.760
at remission	1.0 ±0.1	1.2 ±1.2	0.233
Fibrosis score at index biopsy	2.8 ±1.8	3.6 ±2.0	0.250
Cirrhosis at onset (Ishak 5-6)	3/11 (27.2%)	25/71 (35.2%)	0.442
Histology			
Moderate to severe portal inflammation	9 (81.8%)	51/62 (82.2%)	0.972
Mod to severe interface hepatitis	6 (54.5%)	39/61 (63.9%)	0.554
Mod to severe lobular hepatitis	7 (63.6%	36/61 (59.0%)	0.567
Portal plasma cells	9 (81.8%)	55/61 (90.2%)	0.353
Lobular plasma cells	7 (63.6%)	43/61 (70.5%)	0.448
Portal lymphocytes	9/10 (90%)	51/61 (83.6%)	0.195
Lobular lymphocytes	9/10 (90%)	51/60 (85.0%)	0.563
Portal neutrophils	4/10 (40%)	24/60 (40%)	0.641
Lobular neutrophils	4/10 (40%)	18/60 (30%)	0.385
Portal eosinophils	5/10 (50%)	21/61 (34.4%)	0.272
Lobular eosinophils	4/10 (40%)	16/60 (26.7%)	0.304
Collapse	3 (27.2%)	17/60 (28.3%)	0.628

Cholestatis	1 (9.1%)	9/62 (14.5%)	0.532
Rosettes	3 (27.2%)	13/61 (16.4%)	0.461
Treated	10 (90.9%)	66 (92.9%)	0.591
Prenisolone then azathioprine	7/10 (70%)	46/66 (69.7%)	0.610
Prednisolone+azathioprine	2/10 (20%)	9/66 (13.6%)	0.444
Prednisolone montherapy	1/10 (10%)	10/66 (15.1%)	0.556
Remission	10 (100%)	61 (92.4%)	0.484
Time to remission (wks)	8.00 (2 – 16)	14.00 (2 – 120)	0.321
Relapse	3/5 (60%)	10/12 (83.3%)	0.538
Time to relapse (weeks)	131 (37-216)	14 (1–155)	0.033
Duration of immunosuppression before discontinuation (mths)	19.8 $\pm$11.5	20.2 $\pm$11.6	0.943
Poor outcome	2 (18.2%)	26 (36.6%)	0.316

One patient with AIH treated with azathioprine monotherapy

Table 4. Details of poor outcome events in those with drug induced autoimmune hepatitis (DIAIH) and autoimmune hepatitis (AIH)

Event	DIAIH (n=11)	AIH (n=71)	p value
Liver failure at onset	1 (9.1%)	5 (7.0%)	0.591
Developed cirrhosis during follow up	0 (0%)	6 (8.4%)	0.409
Developed cirrhosis related complications	1 (9.1%)	14 (19.7%)	0.357
Failure to achieve remissions	0/10 (0%)	5/66 (7.5%)	0.484
Need for liver transplant	0 (0%)	2 (2.8%)	0.748
Liver related mortality	0 (0%)	5 (7.0%)	0.650

Some patients had more than one event

Table 5: Nitrofurantoin vs. non-nitrofurantoin drug induced autoimmune hepatitis (DIAIH)

	Nitrofurantoin DIAIH (n=4)	**Non-nitrofurantoin DIAIH (n=7)**
Age (yrs)	76.7 ±3.9	53.6 ±25.3
Duration of drug use prior to abnormal liver tests	36.0 ±9.4	14.5 ±12.7
Drug discontinued prior to specialist review	0 (0%)	5 (71.4%)
Duration between abnormal liver tests -specialist review (wks)	0/4 (0%)	5/7 (71.4%)
ALT (iu/l)	16 (4-80)	6 (0.5-20)
Increase globulins/IgG	303 (115-587)	721 (640-1468)
Definite AIH	4 (100%)	4 (57.1%)
Cirrhosis at onset	0 (0%)	2 (28.5%)
Fibrosis stage	2 (50%)	1 (14.3%)
Portal/lobular neutrophils	3.75 ±2.1	2.3 ±1.6
Lobular eosinophils	0/3 (0%)	4 (57.1%)
Rosettes	0/3 (0%)	4 (57.1%)
Immunosuppression discontinued	3/4 (75%)	0/7 (0%)
Duration of immunosuppression before discontinuation (mths)	2/4 (50%)	3/6 (50%)
Relapse	11.5 ±7.8	20.0 ± 8.5
	0/2 (0%)	3/3 (100%)